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Abstract: Scavenger receptor class B type I (SR-BI) protein is an integral membrane glycoprotein. SR-BI is emerging as a multifunctional protein, which regulates autophagy, efferocytosis, cell survival and inflammation. It is well known that SR-BI plays a critical role in lipoprotein metabolism by mediating cholesteryl esters selective uptake and the bi-directional flux of free cholesterol. Recently, SR-BI has also been identified as a potential marker for cancer diagnosis, prognosis, or even a treatment target. Natural products are a promising source for the discovery of new drug leads. Multiple natural products were identified to regulate SR-BI protein expression. There are still a number of challenges in modulating SR-BI expression in cancer and in using natural products for modulation of such protein expression. In this review, our purpose is to discuss the relationship between SR-BI protein and cancer, and the molecular mechanisms regulating SR-BI expression, as well as to provide an overview of natural products that regulate SR-BI expression.

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SR-BI as a target of natural products and its significance in cancer

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Contents

Abstract

Scavenger receptor class B type I (SR-BI) protein is an integral membrane glycoprotein. SR-BI is emerging as a multifunctional protein, which regulates autophagy, efferocytosis, cell survival and inflammation. It is well known that SR-BI plays a critical role in lipoprotein metabolism by mediating cholesteryl esters selective uptake and the bi-directional flux of free cholesterol. Recently, SR-BI has also been identified as a potential marker for cancer diagnosis, prognosis, or even a treatment target. Natural products are a promising source for the discovery of new drug leads. Multiple natural products were identified to regulate SR-BI protein expression. There are still a number of challenges in modulating SR-BI expression in cancer and in using natural products for modulation of such protein expression. In this review, our purpose is to discuss the relationship between SR-BI protein and cancer, and the molecular mechanisms regulating SR-BI expression, as well as to provide an overview of natural products that regulate SR-BI expression.

Keywords: natural products; scavenger receptor class B type I; cancer; molecular mechanisms.

1. Introduction

Scavenger receptor class B type I (SR-BI) protein was first isolated and identified by Calvo *et al.* [1] based on a sequence closely related to cluster of differentiation 36 (CD36) and lysosomal integral membrane protein (LIMP) analogous-1. The gene of human SR-BI located on chromosome 12, initially named CLA-1, now is called SCARB1 and comprises 13 exons and 12 introns [2]. SR-BI protein is an 82 kDa integral membrane glycoprotein, which (together with LIMP-2) is a member of CD36 superfamily of scavenger receptor proteins [3]. SR-BI has a hairpin-looped structure with two short N- and C-terminal transmembrane domains, two cytoplasmic tails, and a large extracellular loop [4, 5]. A full-length human SR-BI protein contains 509 amino acids, of which a large extracellular domain (ECD) includes 408 amino acids, N- and C-terminal transmembrane domains include 22 and 23 amino acids respectively, as well as N- and C-terminal cytoplasmic domain include 9 and 44 amino acids, respectively [6]. ECD contains multiple sites for N-linked glycosylation of SR-BI [6].

With the conserved function across various species, SR-BI is expressed in many normal and hormonally altered tissues and cell types, including liver, brain, intestine, placenta, and steroidogenic tissues, as well as macrophages, endothelial cells, smooth muscle cells, keratinocytes and adipocytes [2, 7, 8]. SR-BI predominantly expresses in the liver and steroidogenic tissues (adrenal gland, gonads) [9-11]. A previous study suggests that SR-BI protein located in caveolae of ldlA7-SR-BI cells and murine adrenocortical Y1-BS1 cells based on partial colocalization with caveolin-1 [12]. It was reported, however, that SR-BI is majorly localized in clusters of microvillar extensions on the plasma membrane rather than caveolae [13]. Expression of recombinant SR-BI induced the formation of double-membraned channel structures, which increased the uptake of high-density lipoprotein-cholesteryl esters (HDL-CE) [14, 15].

It was demonstrated that the SR-BI is critical to lipoprotein metabolism by mediating CE selective uptake and the bi-directional flux of free cholesterol [16]. SR-BI is emerging as a multifunctional receptor in different cellular types [2]. Hepatic SR-BI selectively takes up HDL-CE for the delivery of cholesterol to bile, which perseveres HDL functions, and is also critical in the clearance of remnant lipoproteins and lipoprotein(a) (Lp(a)) [2, 17]. SR-BI can facilitate the efflux of cholesterol from peripheral tissues including macrophages, then back to liver [17]. In addition, in human and mouse macrophages SR-BI influences autophagy [2]. In both macrophages and endothelial cells, SR-BI could also regulate signaling pathways involved in efferocytosis, cell survival, and inflammation [2]. It was shown that SR-BI mediated the uptake of vitamins as well as viral entry into cells [17]. Recently, SR-BI has also been identified as a potential marker for cancer diagnosis and prognosis [17]. It was reported that abnormal expression of SR-BI may have been associated with tumorigenesis and malignant transformation [18-20]. For example, several patient tumors display higher expression of SR-BI compared to healthy tissue, including adrenal tumors, breast cancer, prostate cancer, lymphoma, nasopharyngeal carcinoma, pancreatic cancer, prostate bone metastasis, and testicular cancer [18-20]. SR-BI could also serve as a promising target for the delivery of therapeutic agents by reconstituted HDL, which directly binds to the SR-BI protein on plasma membrane [19, 20].

Natural products are a promising source for the discovery of new drug leads [21]. Some natural products, including such from plants, fungi and marine sources, are reported to regulate SR-BI protein expression (reviewed in [22]). It was reported that only about 6% of the existing higher plants have been investigated pharmacologically, highlighting that there is still a lot of unexplored potential [23]. In our review, we discuss the relationship between SR-BI protein and cancer, and

the molecular mechanism regulating SR-BI expression, as well as provide an overview of natural products that regulate SR-BI expression.

2. SR-BI functions

2.1 General function

Hepatic SR-BI mediates selective HDL-CE uptake from peripheral tissues and the transhepatic transport of HDL cholesterol into bile regulates the reverse cholesterol transport (RCT) [24-26]. SR-BI is a multifunctional receptor, with recent studies demonstrating that SR-BI affects gastrointestinal, endocrine, reproductive, and cardiovascular pathophysiology [27-32]. SR-BI is involved in both cholesterol uptake and efflux in cells (Figure 1) [33, 34] and has been shown to be the key gatekeeper for specific delivery of cholesterol in human steroidogenic cells [35]. SR-BI promoted the production of glucocorticoids and modulated inflammatory response to protect from endotoxemia and septic death [36, 37]. Along the same line, human patients with SR-BI P297S had a remarkable decrease in urinary steroid secretion, an impaired response to corticotropin stimulation [38, 39], and symptoms resembled with impaired adrenal function. These observations suggest that SR-BI was critical for adrenal steroid synthesis. In addition, SR-BI was shown to be involved in improving inflammation, limiting cell death and regulating efferocytosis of apoptotic cells [2]. In this context, there was increased oxidative stress in SR-BI knockout (KO) mice with dysfunctional HDL [40, 41]. SR-BI increased the protein expression of endothelial nitric oxide synthase (eNOS) in endothelial cells through Akt (also known as protein kinase B (PKB)) and mitogen-activated protein kinase (MAPK) signaling pathway [42-44]. In addition, recent studies demonstrated that SR-BI was responsible for red blood cell maturation, lymphocyte homeostasis, and deficiency of SR-BI resulted in systemic autoimmune disorders by modulating the proliferation of lymphocytes as well as the cytokine production by lymphocytes and macrophages in mice [45-47]. SR-BI also modulated platelet cholesterol contents, platelet activity and thrombosis in dyslipidemia [48, 49]. SR-BI deficient macrophages were defective in autophagy following stress [50], and impaired autophagy, promoted atherosclerosis [51]. Therefore, SR-BI is a receptor with pleiotropic functions and may affect cell functions by mediating the bi-directional flux and net movement of cellular free cholesterol [50]. Future studies need to establish the mechanisms by which SR-BI regulates autophagy in human macrophages, and

whether its role is associated with CE mobilization, macrophage apoptosis and the chronic inflammatory diseases.

Macrophages from patients with loss-of-function SR-BI variants had impaired ability to promote cholesterol efflux [38, 39], suggesting that macrophage SR-BI played an important role in cholesterol homeostasis and chronic inflammatory diseases [52]. Recent epidemiologic studies demonstrated that there was a significant inverse relationship between HDL-cholesterol (HDL-C) levels, HDL particle numbers and risk of cancer development and prognosis [53-56]. Up to now, there are several SR-BI variants identified from human subjects with abnormal HDL-C levels (**Table 1**). Two missense mutations S112F (Serine to Phenylalanine), T175A (Threonine to Alanine) were associated with 37% increased HDL-C in heterozygotes, and P297S (Proline to Serine) was associated with increased HDL-C and reduced cholesterol efflux capacity. It has been shown that a coding variant of SR-BI I179N (Isoleucine to Asparagine) remarkably promoted atherosclerosis in mice [57]. It is worth to note that the new variant P376L (Proline to Leucine) resulted in the complete loss of function, which led to high HDL-C phenotype in human [58]. The heterozygotes had a 2.8-fold increase and the homozygotes had a 6.1-fold increase in large HDL2 particles compared with noncarrier control. The further characterizations of these point mutations of SR-BI, including cell surface expression, binding activity to HDL, and SR-BI signaling pathway were intriguing. The binding ability of SR-BI P376L to HDL was almost completely abolished and the binding ability of P297S to HDL was decreased to half of SR-BI wild type (WT). More importantly, P376L mutation of SCARB1 was associated with increased risk of coronary heart disease (CHD) [58, 59]. However, three rare SR-BI mutations identified from human patients (G319V, V111M, and V32M) were associated with elevated levels of HDL-C, but not with coronary artery disease (CAD) [60]. It remains to be addressed whether there is causal relationship between loss of function mutations of SR-BI and tumor progression.

2.2 SR-BI and cancer

2.2.1 SR-BI and cholesterol metabolism in cancer

Changes in cholesterol metabolism resulted in the alteration of intratumoral synthesis of androgens in castration-resistant prostate cancer [61]. Cytochrome P450 (CYP) 27A1, also known as sterol 27-hydroxylase, is an important enzyme in both the acidic and neutral pathways of bile acid and cholesterol metabolism [62]. CYP27A1 oxidizes the terminal carbon of the

cholesterol isooctyl side-chain to an alcohol and subsequently to an acid introducing R stereochemistry at C-25 [63]. Given its key role in bile acid biosynthesis and cholesterol metabolism, CYP27A1 dysregulation results in dysfunction of cholesterol metabolism and disease in humans [64]. It has been shown that CYP27A1 is significantly down-regulated in human prostate cancer. Restoring CYP27A1 expression in cells reduced tumor growth *in vitro* and *in vivo* model with tumor xenografts [65]. Blocking CYP27A1, which encodes enzyme required for 27-hydroxycholesterol biosynthesis, remarkably prevented metastasis in relevant animal models of cancer, while the cholesterol metabolite 27−hydroxycholesterol promoted breast cancer metastasis through activation of neutrophils [66], which overall points out that cholesterol metabolism plays important roles in cancer development and metastasis. Although there is no study examining the specific mechanisms implying SR-BI in development of cancer [67], it has been demonstrated that cancer cells can take up CE *via* HDL/SR-BI pathway and use it as the substrate to enhance malignant phenotypes [68, 69]. For example, SR-BI was required for uptake of CE from HDL3 in the breast cancer cell line HBL-100 [70]. SR-BI was also needed for selective CE uptake providing cholesterol as precursor for production of steroid hormones and for storage in intracellular CE droplets of Leydig cells from rat testis [71]. HDL also inhibited the activation of sterol regulatory element-binding protein-1 (SREBP-1), which resulted in the transcription of β-Hydroxy β-methylglutaryl-CoA (HMG-CoA) reductase, a key enzyme of cholesterol biosynthesis. It would be intriguing to determine the effect of SR-BI modulation on SREBP-1 activation and cholesterol metabolism for steroid hormones (e.g., androgens and estrogens) in relevant cancers, such as breast cancer and prostate cancer.

2.2.2 The effect of SR-BI on tumor development

Recent studies demonstrated that the protein expression level of SR-BI was correlated with aggressiveness and poor survival in breast and prostate cancer [72]. SR-BI protein expression was shown to be remarkably increased in malignant tissues compared to surrounding disease-free tissues in breast cancer [73], while low SR-BI expression was associated with gastric adenocarcinoma tumor aggressiveness [74]. There was abundant expression of SR-BI in malignant human epithelial cells and hepatoma cells [73, 75, 76]. SR-BI expression was also increased in Leydig cell tumors, prostate cancers, colorectal cancer, ovarian cancer and pancreatic cancer [70, 77]. Specifically, SR-BI promoted the proliferation of the breast cancer cell line MCF-7 through the phosphoinositide 3-kinase (PI3K)/activator protein-1 (AP-1) signaling pathway [68, 78]. Along the same line, overexpression of SR-BI protected breast cancer MCF-7

cells against tumor necrosis factor (TNF)-α-induced apoptosis, whereas expression of the ECD of SR-BI remarkably prevented the cell proliferation [78]. Abolishing SR-BI reduced prostate specific antigen (PSA) secretion and viability of prostate cancer cells [79]. Pharmacological inhibition of SR-BI reduced breast cancer cell proliferation, prevented tumor growth in xenograft tumor mice by inhibition of angiogenesis and Akt activation [68, 69]. In addition, SR-BI was involved in the melanoma pigmentation pathway, and deficiency of SR-BI decreased the melanocyte master regulator microphthalmia-associated transcription factor (MITF) and inhibited extracellular vesicle release in human melanoma [80]. Taken together, SR-BI plays an important role in cancer cell proliferation and apoptosis, thus, has a potential major impact in carcinogenesis and metastasis.

2.2.3 PDZK1 and SR-BI in cancer

The SR-BI scaffold protein PDZK1 is critical for the cell surface expression of SR-BI [81]. KO of PDZK1 resulted in a post-transcriptional, tissue-specific reduction in SR-BI protein level, and there was an increase in plasma total HDL-C and the size of HDL particles in PDZK1 deficient mice, which exhibited the similar phenotypes to those observed in SR-BI KO mice [82]. PDZK1 belongs to the estrogen-regulated genes expressed in hormone-responsive breast cancer [83]. Recent study demonstrated that PDZK1 promoted estrogen receptor (ER)-α-mediated growth of breast cancer, indirectly regulated by insulin-like growth factor-1 receptor (IGF-1R), therefore identifying a new oncogenic role of PDZK1 in breast cancer [84]. Furthermore, knockdown of PDZK1 abolished ER-dependent cell growth and decreased c-Myc expression in MCF-7 cells, whereas overexpression of PDZK1 promoted cell proliferation through c-Myc. Previous studies demonstrated that expression of breast cancer resistance protein (BCRP, gene symbol ABCG2), an ATP-binding cassette (ABC) efflux transporter, was reduced in PDZK1 KO mice [85]. PDZK1 was highly overexpressed in ER-positive breast cancers as compared with ER-negative breast cancers, which probably affected SR-BI function and cancer development. However, whether the effect of PDZK1 on the growth of cancer cells is dependent on SR-BI needs to be further studied. Further studies need to address whether co-transfected cells with PDZK1 and SR-BI mutants affects cancer cell surface expression of SR-BI mutants (e.g., P297S, P376L) to regulate cancer cell cholesterol metabolism and cell proliferation.

2.2.4 Effects of SR-BI on macrophage polarization and cholesterol efflux in tumor-associated macrophages (TAMs) and tumor progression

Mounting evidence supported that TAMs were associated with tumor progression, invasion and metastasis, and poor prognosis [86]. At the initial stage of tumor development, TAMs were observed to exhibit a pro-inflammatory gene profile, which is distinct from that of naive resident macrophages. However, TAMs rapidly took on a substitute phenotype with tumor promoting immunosuppressive function within the tumor microenvironment [87, 88], although there was a specific subsets of macrophages with intrinsic tumoricidal activity [86]. In established tumors, TAMs were observed to display a phenotype similar to resident macrophages, which indicated a dynamic reprogramming of TAM phenotype during tumor progression. Recent study has shown that SR-BI deficiency promoted pro-inflammatory macrophage phenotype and upregulated pro-inflammatory gene expression. SR-BI KO macrophages promoted the M1 phenotype and failed to exhibit an M2 phenotype. Furthermore, SR-BI deficiency promoted activation of ERK1/2 MAPK signaling in macrophages stimulated with LPS [89]. These studies demonstrate SR-BI regulates macrophage phenotype switching and cholesterol metabolism. Recent studies have shown that an unexpected influence for membrane-cholesterol efflux resulted in driving TAM-regulated tumorigenesis (**Figure 2**) [90]. Interestingly, KO of ABCA1/G1 restored the tumor-promoting functions of TAMs. Ovarian cancer cell-derived hyaluronic acid (HA) remarkably increased membrane cholesterol efflux of TAMs [90], which was associated with increased interleukin (IL)-4-mediated signaling pathway and inhibition of interferon (IFN)γ-induced gene expression, leading to transcriptional and functional reprogramming of TAMs. Specifically, reduction of membrane cholesterol in macrophages promoted PI3K activity and mammalian target of rapamycin complex (mTORC)2-mediated Akt phosphorylation. PI3K was recently shown to be an essential pathway to preserve the pro-tumor functions of TAMs [91], and mTORC2 have been associated with IL-4-regulated macrophage activation in different contexts [92-94]. The possible mechanistic scenario is that cholesterol-rich membrane micro-domains are required to recruit negative mediators of PI3K activity, such as the lipid phosphatase - the SH-2 containing inositol-5'-polyphosphatase-1 (SHIP-1). SHIP-1 may reside in detergent resistant membrane fractions [95], and it is known to inhibit IL-4 signaling in macrophages [93]. However, it remains to be determined whether SR-BI contributes to membrane cholesterol efflux in TAMs and whether reprogramming of TAMs affects tumorigenesis through SR-BI. This will be an important area of investigation, that might provide exciting new insights into the lipoprotein metabolism, tumor associated macrophages and tumor progression as well. Taken together, SR-BI is critical for regulating the cholesterol homeostasis and inflammatory response. Identification of the detailed mechanism by which SR-BI functions, including its adaptor proteins, signaling molecules, and

transcriptional regulators, will lay a solid foundation for potential discovery of novel diagnostic or therapeutic approaches for cancer.

3. Mechanisms of SR-BI expression regulation

The SR-BI expression can be regulated by transcriptional factors, other endogenous factors, noncoding RNAs (ncRNA), as well as its accessory proteins at transcriptional, post-transcriptional, or post-translational levels (**Table 2** and **Figure 3**).

3.1 Transcriptional factors

SR-BI is regulated by many transcriptional factors, such as the liver X receptor (LXR), peroxisome proliferator-activated receptor (PPAR), farnesoid X receptor (FXR), retinoid X receptor (RXR), SREBP, ER, steroidogenic factor-1 (SF-1), hepatic nuclear factor 4α (HNF4α), liver receptor homolog-1 (LRH-1), prolactin regulatory element-binding protein (PREB), forkhead box protein O (FoxO), dosage-sensitive sex adrenal hypoplasia congenital critical region on the X chromosome, gene-1 (DAX-1), Yin Yang-1 (YY-1), pregnane X receptor (PXR), and signal transducer and activator of transcription (STAT).

3.1.1 LXR

The LXRα and β form heterodimers with the RXR for transcriptional activity [96]. Oxysterol-activated LXRα/RXR and LXRβ/RXR induced SR-BI transcription in human and murine hepatoma cell lines, and in 3T3-L1 preadipocytes by binding to putative LXR response element (LXRE) in the promoter region to induce SR-BI-promoter activity, independently of SREBP-1 [97]. On the contrary, LXR reduced levels of SR-BI in Caco-2/TC7 cells *via* a post-transcriptional mechanism that involves microRNAs (miR) [98]. *In vivo* it was demonstrated that treating normolipidemic hamsters with LXR agonist GW3965 did not effectively induce the mRNA and protein levels of SR-BI in the liver [99]. Furthermore, another animal study indicated that LXR activation by its ligand TO901317 reduced SR-BI protein, but not mRNA levels in hepatic membranes of C57Bl/6J mice, which is not due to changing PDZK1 [100]. The contradictory observed effects of LXR on SR-BI expression possibly is due to the different cell types and different animal models.

3.1.2 PPAR

The PPARα can form heterodimers with the RXR to regulate gene expression [101]. PPARα/RXR increased the activity of the SR-BI promoter in the human bladder HTB-9 cells, human promyelocytic leukemia HL-60 cells, and human monocytic leukemia THP-1 cells by binding to a PPAR response element (PPRE) in the SR-BI promoter [102]. The PPARα specific ligand WY14643 increased SR-BI level in the rat hepatocytes and HepG2 hepatoma cells, as well as liver endothelial cells [103]. The influence of PPARα on hepatic SR-BI expression in animal studies is controversial. In hamsters, dietary polyunsaturated fatty acids (PUFA, a strong inducer of PPARα) for 6 weeks, up-regulated hepatic SR-BI mRNA and protein levels [104]. SR-BI expression was also increased in atherosclerotic lesions of apolipoprotein (apo)E-deficient mice treated with the PPARα ligand Wy14643 [105]. On the contrary, treatment with fibrate, a potent PPARα agonist, suppressed SR-BI protein expression in the liver without changing steady state of mRNA in both wild-type C57BL/6 mice [106] and PDZK1-deficient mice [107], which may be due to down-regulation of Clamp, a putative SR-BI-stabilizing protein found in the hepatic plasma membrane, but independent of PDZK1. Moreover, fenofibrate-decreased SR-BI stability was also independent of the proteasome, calpain protease, or the lysosome [107]. It remains to further identify the precise mechanisms regulating hepatic SR-BI by PPARα. Noteworthy, in human, SR-BI mRNA level in circulating mononuclear cells was not changed by fenofibrate [108].

A selective PPARγ agonists induced SR-BI expression in rat hepatocytes, endothelial cells, Hepa 1c1c-7 and Kupffer cells by a mechanism involving co-activation of HNF4α [103]. In addition, the PPARγ agonist thiazolidinediones increased hepatic SR-BI mRNA and protein levels in HepG2 by binding to the SR-BI promoter region to induce SR-BI promoter activity [109]. *In vivo*, the PPARγ agonist GW7845 (20 mg/kg/day) significantly increased SR-BI protein expression in adipose tissue, but not liver of C57BL/6 mice [110]. SR-BI expression was also increased in atherosclerotic lesions of apoE-deficient mice treated with the PPARγ ligand PG-J2 [105].

3.1.3 FXR

The regulation of SR-BI expression by FXR is contradictory. On the one hand, bile acid (chenodeoxycholic acid)-activated FXR/RXR suppressed SR-BI expression in hepatocytes by inducing the expression of the Small Heterodimer Partner (NR0B2, SHP), which inhibited LRH-1-transactivation of SR-BI [111]. It was assumed that chenodeoxycholic acid influenced SR-BI

possibly through multiple pathways, since it also activated other gene expression regulatory pathways besides selective agonism of FXR [112, 113]. A specific FXR agonist GW4064 also down-regulated the expression of SR-BI protein in Huh7.5 cells [114]. On the other hand, it was reported that GW4064 induced mRNA and protein levels of hepatic SR-BI *in vitro* and *in vivo* by increasing HNF4α protein expression, which directly targeted HNF4α response elements in the SR-BI promoter [115]. Similarly, an FXR agonist obeticholic acid increased hepatic SR-BI mRNA and protein levels in hyperlipidemic hamsters, but not in normolipidemic hamsters [116]. FXR can directly bind to the intronic inverse repeat separated by one nucleotide (IR1), a FXR response element (FXRE), in the mouse SR-BI promoter to increase its expression [117]. In human HepG2, FXR can bind to a directed repeat DNA motif DR8 to up-regulate SR-BI expression [118]. In addition, in the FXR-deficient mouse model SR-BI expression was significantly decreased [119].

Recently, it was demonstrated that FXR and LXR bound to their recognition sequences within the intronic region (containing FXRE (IR-1) and LXRE) of the SR-BI gene and transactivated the SR-BI reporter gene in a synergistic manner [99]. In *in vivo* model, combined treatment of FXR and LXR agonists significantly increased the mRNA and protein levels of SR-BI in the liver, while FXR or LXR agonists alone did not have such effect [99]. Although the intronic FXRE and LXRE regulatory region was not conserved in the human SR-BI genomic sequence, higher mRNA expression level of SR-BI was observed in human primary hepatocytes and HepG2 cells exposed to combined treatment of FXR and LXR agonists, compared with individual agonist treatment [99].

RXR forms heterodimers with the LXRα, LXRβ, PPARα, and FXR for transcriptional regulation of SR-BI [97, 102, 111]. The RXR agonist 9-*cis* retinoic acid induced the expression of SR-BI mRNA in human umbilical vein endothelial cells (HUVECs) [120].

3.1.4 SREBP

SREBP-1a is a key protein in the transcriptional regulation of some genes by sterols [121]. SREBP-1a activated transcription of rat SR-BI by binding to sterol response elements (SRE) in the promoter of SR-BI in response to altered intracellular sterol levels [121]. SREBP-1a requires the presence of a coactivator like simian-virus-40-protein-1 (Sp1) to promote maximum activation of the SR-BI promoter [122]. SREBP-1a is also a potential coactivator of the estrogen-ER-dependent upregulation of SR-BI gene [123].

SREBP-2 increased SR-BI mRNA and protein levels in transfected HEK293 and HepG2 cells by binding to SR-BI promoter [124]. This study also suggests that SREBP-2 is a more potent inducer for SR-BI promoter activity than the SREBP-1a isoform in the studied models [124]. On the contrary, in SREBP-1a and -1c transgenic mice on normal chow, hepatic SR-BI was transcriptionally down-regulated [125].

3.1.5 ER

Estradiol (E2) significantly increased SR-BI promoter activity by activation of ER-α and -β and following binding to ER element (ERE) 1, 2, and 4 *in vitro* [123]. Along with ERs, mixed-lineage leukemia (MLL) histone methylases, including MLL1 and MLL2, play important roles in E2-mediated SR-BI activation, through binding to SR-BI promoter and further control of the assembly of transcription pre-initiation complex and RNA polymerase II recruitment [126]. MLL2 knockdown in mice reduced SR-BI expression in mouse liver [126]. In addition, high-dose estrogen treatment, however, dramatically reduced SR-BI in the liver and increased SR-BI expression in the adrenal gland and corpus luteal cells of the ovary in rats [127]. Further study indicated that in the rat liver the decrease in SR-BI by 17α-ethinyl estradiol treatment was due to the estrogen-increased low-density lipoprotein receptor (LDLR) activity, while in the adrenal glands the increase in SR-BI was due to inhibition of adrenocorticotropic hormone (ACTH) production [128]. Recently, it was reported that estrogen caused down-regulation of endothelial SR-BI in human coronary artery endothelial cells depending on G-protein-coupled ER (GPER), but there was no effect on SR-BI expression in liver cells because of low expression of GPER in hepatocytes [129]. The estrogen regulation mechanisms of the SR-BI gene were reviewed elsewhere [130].

3.1.6 SF-1

SF-1, an orphan member of the nuclear hormone receptor gene family, plays a key role in the regulation of steroidogenesis [131]. SF-1 was shown to directly bind to the SR-BI promoter in a sequence-specific manner [131], and activated transcription of the SR-BI gene in both human HTB9 bladder carcinoma and mouse Y-1 tumor cells, which effect was enhanced by cyclic AMP (cAMP) by increasing phosphorylation of SF-1 at Ser 430 by PKA [132]. Furthermore, no SR-BI mRNA was detected in the gonadal ridge of day 11.5 SF-1 KO embryos, suggesting SF-1 also regulated SR-BI *in vivo* [133].

3.1.7 HNF4α

In cultured hepatocytes, HNF4α increased SR-BI expression at both mRNA and protein levels, which can be inhibited by a PPARγ antagonist BADGE [134]. *In vivo*, hepatic overexpression of HNF4α upregulated SR-BI mRNA and protein levels in rat liver possibly by the upregulation of PPARγ [134].

3.1.8 LRH-1

LRH-1 induced SR-BI expression by binding to an LRH-1 response element in the promoter of SR-BI, which associated with histone H3 acetylation on the SR-BI promoter *in vitro* [135]. *In vivo*, the SR-BI mRNA levels were decreased in the livers of the heterozygous LRH-1-KO mice [135]. LRH-1 was also involved in FXR/RXR-suppressed SR-BI expression by bile acid (chenodeoxycholic acid) in hepatocytes through inhibition of LRH-1-transactivation of SR-BI [111].

3.1.9 PREB

PREB is a transcription factor that regulates prolactin promoter activity in the rat anterior pituitary [136]. Overexpression of PREB using a PREB-expressing adenovirus increased the expression of the SR-BI protein in the adrenocortical cell line Y-1 cells by binding to the PREB-responsive *cis*-element in the SR-BI promoter under conditions that increase cellular cAMP levels [137].

3.1.10 FoxO

Recently, it was reported that mice with liver-specific triple FoxO KO (FoxO1,3,4) had substantially decreased hepatic SR-BI expression [138]. In our experiments, knockdown of FoxO1 did not change SR-BI mRNA and protein expression in primary human aortic endothelial cells.

3.1.11 DAX-1

The nuclear receptor NR0B1 (DAX-1) plays an important role in adrenal development [6]. DAX-1 repressed activation of the SR-BI promoter not only through interaction with SREBP-1a to prevent subsequent binding of SREBP-1a to SR-BI promoter, but also by formation of a complex with SF-

1 protein on the DNA to prevent activation of SR-BI promoter in transfected adrenal Y-1, HTB-9, and HepG2 cells [139].

3.1.12 YY-1

The ubiquitous zinc finger transcription factor YY-1 has been shown to repress several sterol-responsive gene promoters [140]. YY-1 also repressed the activity of the SR-BI promoter, and attenuated the transcriptional synergy caused by the combined actions of SREBP-1a and a co-activator like simian-virus-40-protein-1 (Sp1) by inhibiting the binding of SREBP-1a to SR-BI promoter in transfected HTB9 cells [141].

3.1.13 PXR

SR-BI was inhibited by the PXR activators rifampicin and lithocholic acid in HepG2 cells, as well as by pregnenolone 16α-carbonitrile (PCN) in primary rat hepatocytes [142]. *In vivo* study demonstrated that PCN decreased hepatic SR-BI level in ApoE3-Leiden (E3L) and E3L.CETP mice [143].

3.1.14 STAT

The mutagenesis of a STAT1/STAT2 response element in the SR-BI promoter abolished the ability of IFNα to suppress SR-BI promoter activity [144].

3.2 Endogenous factors

3.2.1 Hormones

In steroidogenic cells, the expression of SR-BI is regulated by trophic hormones in concert with the regulation of steroid hormone production [145]. The protein and mRNA expression of SR-BI were increased in cultured murine Y1-BS1 adrenal cells treated with ACTH [146]. ACTH-stimulation of SR-BI can be mediated through cAMP-increased binding of SF-1 to the SR-BI promoter [17]. It was reported that *in vivo* ACTH treatment increased SR-BI protein expression in adrenal glands of C57BL/6 mice, which was suppressed by treatment with the glucocorticoid

dexamethasone phosphate [147]. In addition, in the acute phase of adrenocortical steroidogenesis, ACTH rapidly stimulated the metabolism of sphingolipids and the secretion of sphingosine-1-phosphate (S1P), which further increased the expression of SR-BI [148]. ACTH treatment can modulate SR-BI expression at the transcriptional and posttranscriptional levels, and the underlying mechanisms were recently summarized by Shen *et al.* [149].

Glucocorticoids suppressed SR-BI expression in adrenocortical H295R and ovarian SKOV-3 cells depending on the glucocorticoid receptor (GR), which cannot directly bind to the SR-BI promoter [150]. Further study showed that glucocorticoids repressed SR-BI expression through the region between nucleotides -201 and -62 in the human SR-BI promoter, which included putative binding sites for transcriptional repressors for SR-BI gene transcription [150]. *In vivo*, SR-BI mRNA level was upregulated in adrenals of corticosterone-deficient mice, whereas corticosterone treatment inhibited SR-BI gene expression in these mice [150]. Treatment with metyrapone, an inhibitor of corticosterone synthesis, increased SR-BI mRNA level in adrenals from wild-type mice [150]. On the contrary, the glucocorticoid dexamethasone increased SR-BI mRNA expression in primary rat hepatocytes, which was reduced by the addition of the anti-glucocorticoid mifepristone [151]. The stimulation effect of dexamethasone was not observed in HepG2 cells and THP-1 macrophages [151].

Angiotensin II (Ang II) was reported to suppress SR-BI expression in human umbilical vein endothelial cells by PI3K/Akt/FoxO1 pathway by downregulating SR-BI promoter activity, which was rescued by the Ang II receptor type 1 (AT1) blocker olmesartan [152]. Ang II treatment also down-regulated SR-BI protein and mRNA expression in a mouse proximal tubular cell line MCT cells, which effect was attenuated by an AT1 antagonist, but not an AT2 antagonist [153]. *In vivo*, Ang II-infusion into rats induced a significant decrease of SR-BI protein expression in isolated tubules [153]. On the contrary, in the human adrenocortical carcinoma cell line NCI-H295R cells Ang II stimulated SR-BI mRNA and protein expression by activation of the human SR-BI promoter [154].

Insulin increased both mRNA and protein levels of SR-BI in polarized CaCo-2 cells, which effects were abrogated by PI3K, Akt, or mTOR pharmacological antagonism [155]. *In vivo*, SR-BI expression was increased in all intestinal segments in two diet-induced animal models of insulin resistance (fructose-fed hamster and high-fat-fed mouse) [156]. It was reported that IGF-1 decreased SR-BI mRNA and protein levels by the PI3K/Akt signaling pathway in THP-1-derived

macrophages [157]. Similarly, IGF-1 suppressed expression of SR-BI in cultured HepG2 cells [158]. Consistent with *in vitro* data, in rats infused with IGF-I for 7 days SR-BI mRNA level was decreased [158]. The PI3K/Akt pathway participated in IGF-1-inhibited SR-BI expression by suppression of activity of the human SR-BI promoter [158]. Pregnancy-associated plasma protein-A (PAPP-A)-decreased SR-BI expression in THP-1 macrophage-derived foam cells was mediated through the IGF-1/PI3K/Akt signaling pathway [158]. *In vivo*, PAPP-A knockdown by PAPP-A shRNA in apoE-deficient mice reduced the IGF-1 levels, repressed the PI3K/Akt pathway, and in turn increased SR-BI expression in both aorta and peritoneal macrophages [159].

It was also reported that thyroid hormone receptor β (TRβ), hepatic lipase (HL), testosterone and leptin also can regulate SR-BI expression. Activation of TRβ by its agonist GC-1 increased SR-BI expression [160]. Inhibition of HL in mice up-regulated the SR-BI expression in adrenal gland [161, 162]. Testosterone up-regulated SR-BI mRNA and protein levels in both cultivated HepG2 cells and primary human monocyte-derived macrophages (HMDMs) [163]. In leptin-deficient mice, the hepatic SR-BI protein level was reduced [164]. Treatment with leptin for 2 days dose-dependently increased hepatic SR-BI protein and mRNA levels in leptin-deficient mice [164].

A recent study suggested that DNA methylation may participate in hormonal regulation of SR-BI expression in a tissue-specific manner [145]. The SR-BI gene contains one CG island (CGI) in its promoter and seven CGIs in its intronic regions [145]. It was demonstrated that the seven intron CGIs were methylated differentially in mouse adrenal Y-1 cells, mouse Leydig tumor cells (MLTCs), ovarian granulosa cells, and mouse liver Hepa 1-6 cells through N(6), 2'-O-dibutyryladenosine3':5'-cyclic monophosphate regulation [145]. In addition, DNA hypermethylation of the SR-BI promoter in rat fetal adrenal glands may lead to decreased SR-BI expression [165].

3.2.2 Other endogenous factors

The cytokine IFNα suppressed SR-BI expression in HepG2 cells by a pathway involving phosphorylation of STAT1/STAT2, which in turn bound to STAT1/STAT2 response element in the SR-BI promoter to inhibit SR-BI promoter activity [144]. The second messenger cAMP increased SR-BI mRNA expression in transfected 293T cells, human granulosa SVOG-4o cells, and in primary cultures of rat theca-interstitial cells by the cAMP response element binding protein (CREB), which directly bound to promoter of SR-BI to induce its activation [166].

It was shown that administration of liver growth factor (LGF) to ethane dimethanesulfonate (EDS)-treated rats resulted in a remarkable increase in the levels of SR-BI protein [167]. Hormone-sensitive lipase (HSL) KO male mice have increased SR-BI protein expression, but not mRNA levels in the testis [168]. The molecular mechanisms by which LGF and HSL regulated SR-BI expression remain to be further studied.

It was shown that high glucose (25-30 mM) decreased SR-BI mRNA and protein levels in HMDMs [169], Caco-2/15 cells [170], and HepG2 cells [171]. Further study indicated that glucose-induced suppression of hepatic SR-BI expression was partially mediated by the activation of the p38 MAPK-specificity protein-1 pathway [171]. *In vivo*, hepatic expression of SR-BI was lower in diabetic rats than in euglycemic rats [171]. On the other side, in J774A.1 macrophage-like cells, high glucose (30 mM) increased SR-BI mRNA and protein expression [172]. Furthermore, SR-BI mRNA and protein expression were significantly increased in mouse peritoneal macrophages (MPM) harvested from C57Bl/6 diabetic mice, compared to MPM from control non-diabetic mice [172]. In addition, one study showed that high glucose (25 mM) did not modify SR-BI abundance in polarized CaCo-2 cells [155].

3.3 NcRNA

Recently, ncRNA, such as miRs have been investigated in the regulation of SR-BI expression. MiRs regulate SR-BI expression at the post-transcriptional level by directly binding to complementary sequences in the 3'-untranslated regions (3'-UTR) of SR-BI mRNA, causing RNA destabilization or translational repression. The miRs regulating SB-BI expression include miR-24, miR-96, miR-125a, miR-185, miR-217, miR-223, and miR-455.

Recent work demonstrated that miR-24 inhibited SR-BI protein expression in HepG2 and THP-1 cells by specifically targeting the 3'-UTR of SR-BI mRNA [173]. Another group also indicated that miR-24 decreased SR-BI level in steroidogenic cells MLTC and Y-1, as well as HepG2 cells [174]. *In vivo*, miR-24 administration decreased hepatic SR-BI expression and promoted atheromatous plaque formation in apoE-deficient mice [173]. It was shown that the level of SR-BI expression was repressed by miR-96, miR-185, and miR-223 in HepG2 cells, which directly targeted the 3'-UTR of SR-BI mRNA with a coordinated effect [175]. Furthermore, the decrease of miR-185 and miR-96 is related to the increase of SR-BI in the liver of apoE-deficient mice exposed to a high fat

diet (HFD) [175]. Another study found that miR-125a and miR-455 negatively regulated mRNA and protein levels of SR-BI in the rat Leydig tumor R2C cells and the cAMP-sensitive cells MLTCs [176]. Further study showed that miR-125a, but not miR-455 inhibited expression of hepatic SR-BI in the mouse and rat livers as well as the mouse hepatic cell line Hepa 1-6 [176]. It was reported that miR-217 mimic administration in apoE-deficient mice significantly down-regulated SR-BI mRNA levels [177]. The mechanisms of miR-217-mediated regulation of SR-BI are not yet clear. Moreover, other miRs regulating the SR-BI expression remain to be further explored.

3.4 Accessory proteins interacting with SR-BI protein

Accessory proteins, PDZK1/Na+/H+ exchanger regulatory factor 3 (NHERF3), NHERF1 and NHERF2, can interact with SR-BI, which in turn can regulate the expression of SR-BI at the post-translational level [17]. PDZK1 is expressed in liver, kidney and gut, but not in steroidogenic tissues [112], whereas NHERF1 and NHERF2 are expressed in steroidogenic cells of the adrenal gland, ovary and testis, as well as the liver [17, 178]. All NHERFs contain multiple “PDZ” domains (postsynaptic density (PSD-95), Drosophila disc large tumor suppressor (Dlg-1), and zona occludense-1 protein (ZO-1)) [6, 179], which bind and interact with the PDZ recognition motif in SR-BI to regulate its protein stability [180, 181]. It was reported that SR-BI protein expression in PDZK1-deficient mice was reduced by 95% in the liver, 50% in the proximal intestine, but not affected in steroidogenic organs [178]. On the contrary, NHERF1 and NHERF2 overexpression down-regulated the SR-BI protein expression in liver and steroidogenic tissues/cells [180]. The regulation exerted by NHERFs on SR-BI expression was summarized by several reviews [6, 17, 112]. The nuclear receptors LXRα- and PXR-regulatory action on SR-BI could also be through affecting PDZK1. One study indicated that activation of LXRα enhanced mRNA expression of PDZK1 in HepG2 cells, while activation of PXR reduced the protein amount of PDZK1 [182].

4. Natural products regulating SR-BI

Natural products have been historically proven to be a promising pool of structures for drug discovery [21], and significant efforts have recently been taken to explore the SR-BI regulatory potential of natural products originating from traditional medicine or dietary source [183, 184]. Details of representative natural products are listed in **Table 3**.

4.1 Polyphenols

Polyphenols are the most well-known natural products which possess many bioactivities, including regulation of SR-BI expression [185, 186]. This class of phytochemicals is chemically characterized by common polyhydroxylated phenolic moieties. They include two main classes: flavonoids and non-flavonoids [187, 188].

4.1.1 Flavonoids

4.1.1.1 Flavonols

Some of the major flavonol compounds are quercetin and kaempferol. Onions, broccoli, apples, green tea, and black grapes are the sources of these flavonols. Most research on flavonols related to SR-BI expression focused on cellular cholesterol efflux [189]. Quercetin significantly increased the expression of SR-BI in HepG2 cells in a concentration- and time-dependent manner [190]. Moreover, quercetin induced the expression of SR-BI and the selective uptake of HDL-C through PPARγ pathway [190]. Kaempferol, extracted from a classic Chinese medicine *Carthami Flos* which is used for promoting blood circulation and removing blood stasis, up-regulated SR-BI expression and further inhibited oxidized LDL (oxLDL) uptake in macrophages [191].

4.1.1.2 Flavanols

The dietary consumption of polyphenols consists principally of 80% flavanols, which mainly include catechins and tannins [187, 188]. Treatment with catechins (30 mg/kg) in rats increased mRNA expression of SR-BI in aorta and in liver, which resulted in anti-atherogenic properties [192]. 1,2,3,4,6-penta-*O*-galloyl-β-D-glucose (PGG) is a prototypical gallotannin and the key compound in the biosynthetic pathway of hydrolysable tannins. It is highly enriched in medicinal herbals such as *Rhus chinensis*, *Paeonia lactiflora*, and *Acer truncatum*. PGG increased expression of SR-BI in both J774 and THP-1 macrophages [193].

4.1.1.3 Flavones

Flavones include apigenin, chrysin, diosmin, luteolin and baicalein, which could be detected in fruits, nuts, and vegetables [194]. Apigenin-7-*O*-β-D-glucuronide, which is present in *Cirsium japonicum* DC, was reported to enhance the expression of SR-BI and inhibit the uptake of oxLDL by macrophage [195]. Luteolin, a bioactive compound abundant in celery and green bell pepper, induced SR-BI expression and further inhibited oxLDL-elicited macrophage foam cell formation [196].

4.1.2 Non flavonoids

4.1.2.1 Phenolic acids

Phenolic acids are widely found in a variety of nuts and fruits, such as raspberries, grapes, strawberries, walnuts, cranberries, and black currants. These compounds exist predominantly as hydroxycinnamic acids (*p*-coumaric acid, caffeic acid, ferulic acid, chlorogenic acid, and sinapic acids) and hydroxybenzoic acids (gallic acid, salicylic acid, protocatechuic acid, ellagic acid, gentisic acid) or alternatively as conjugated forms [197]. Caffeic acid and ferulic acid, the major phenolic acids isolated from coffee, were proven to regulate SR-BI expression, and have anti-atherogenic properties by enhancing HDL-mediated cholesterol efflux from the macrophages [198]. Ellagic acid regulated PPARγ-SR-BI signaling pathway and in turn downregulated macrophage lipid uptake and suppressed foam cell formation from macrophages with oxLDL treatment [199].

4.1.2.2 Stilbenes

Among stilbenes, resveratrol (3,5,4'-trihydroxy-*trans*-stilbene) is the well-studied stilbenoid. Resveratrol is a natural polyphenolic stilbene found in grape skin, nuts, and some herbal medicines, such as *Fallopia japonica* [200]. Resveratrol is widely used as an anti-cancer, anti-oxidant and anti-atherosclerosis dietary supplement [201]. Many molecular actions of resveratrol rely on the activation of AMP-activated protein kinase (AMPK) and sirtuin 1 (SIRT1) [202]. It has been demonstrated to be responsible for the protective effect in different pathological processes characterized by hyperlipidemia [203]. In human keratinocytes, resveratrol was able to increase SR-BI protein level in a dose-dependent manner [204]. Resveratrol has also been proved to decrease serum cholesterol level through induction of major cholesterol transporters (ABCA1, ABCG1 and SR-BI) in both human macrophages and endothelium, which in turn stimulated

removal of free cholesterol and cholesterol esters [205]. Although positive effects of polyphenols have been observed in preclinical studies, it is important to point out that, in humans, most of the bioactive effects depend on the absorption and metabolism of these compounds [206-208]. Thus, further clinical studies are warranted to determine the bioactivity and biotransformation of polyphenols toward regulation of SR-BI expression in humans [209].

4.1.3 Clinical study

SR-BI plays a very important role in regulation of cholesterol metabolism in humans. Hepatic SR-B1 mediates the selective uptake of HDL-CE into the liver for excretion in the bile and ultimately the faeces to decrease cholesterol level. Thus, most of clinical studies focus on the effect of compounds on the levels of total cholesterol, LDL-cholesterol, and HDL-cholesterol. Polyphenols were reported to exhibit the beneficial effects on hyperlipidemia while contrary opinions also exist. Dietary flavonoids were regarded as related factors of reduced total and LDL cholesterol and increased HDL fraction [210-214]. In the Moli-sani cohort, higher intake of polyphenols was associated with lower total and LDL cholesterol and higher HDL cholesterol levels [215]. In a subset cohort of the ATHENA study, total polyphenol intake was not associated with an improved lipid profile, but individuals with the serum paraoxonase/arylesterase 1 single nucleotide polymorphisms rs854549 and rs854552 showed a positive association between HDL cholesterol levels and total polyphenol intake [216]. A 4-week, double blind, randomized, placebo controlled trial involving 32 type 2 diabetes patients showed that flavonoid-rich grape seed extracts significantly improved the biomarkers of glycemia and hyperlipidemia [217]. A randomized, double-blind, placebo controlled trial with 48 diabetes patients revealed that a 12-week daily supplementation of pycnogenol (125 mg), could reduce CVD risk factors (such as lowering cholesterol level) [218]. Red wine polyphenols were found to have a beneficial effect on plasma concentrations of lipoprotein and cholesterol in a randomized clinical trial involving 67 men with high cardiovascular risk [219]. In a randomized, controlled, cross-over study, a single dose of flavonoid-rich black tea was found to significantly reduce blood glucose and cholesterol in men and women without history of cardiovascular disease (CVD) or diabetes [220]. Another randomized controlled trial was launched in subjects with obesity and metabolic syndrome following an 8-week supplementation with green tea beverage (928 mg catechins) or encapsulated green tea extracts (870 mg catechins). Green tea consumption showed a decreasing trend in LDL cholesterol [221, 222]. The blood cholesterol-lowering effects of

resveratrol were observed in type 2 diabetes [223], and in obese men with impaired insulin action [224].

On the contrary, a prospective cross-sectional study conducted on 38,018 women suggested there was no relationship between flavonols or flavones consumption and the risk of CVD [225]. Two randomized, double-blind, placebo controlled trials showed the supplementation of polyphenol might not improve cholesterol profile in non-diabetic subjects with impaired glucose tolerance [226]. Long-term randomized trials are warranted to reveal the effects of polyphenols in humans.

Ongoing and completed clinical trials have reported the safety and efficacy of polyphenols as anticancer agents [227]. A phase I study showed the efficacy and safety of muscadine grape skin extract (which contains ellagic acid, quercetin, and resveratrol) in men with biochemically recurrent prostate cancer [228]. Flavonoids might be specific components that could reduce ovarian cancer risk. 171,940 Nurses' Health Study participants were followed to examine associations between intakes of total flavonoids, including their subclasses flavanones, flavonols, anthocyanins, flavan-3-ols, flavones, and polymeric flavonoids, and risk of ovarian cancer by using Cox proportional hazards models. Participants in the highest quintiles of flavonol and flavanone intakes had modestly lower risk of ovarian cancer, especially the association for flavanone being stronger for serous invasive and poorly differentiated tumors [229]. Quercetins, which belongs flavonol subclass, are also proved to be related with ovarian cancer progress [230].

4.2 Alkaloids

4.2.1 Purine alkaloids

Purine alkaloids are produced in a variety of plant species, *e.g.*, coffee, tea and cacao. The most abundant purine alkaloid is caffeine. Prenatal caffeine ingestion (PCI) induced intrauterine growth retardation (IUGR). Further studies indicated that caffeine inhibited SR-BI-mediated cholesterol uptake in fetal adrenals, subsequently decreased glucocorticoid synthesis and induced IUGR. Moreover, caffeine induced long-term alterations in SR-BI expression and glucocorticoid synthesis in adult male offspring rat adrenals [231].

4.2.2 Benzylisoquinoline alkaloids

Benzylisoquinolines are mainly contained in basal angiosperms, *e.g.*, in members of the *Berberidaceae, Fumariaceae, Papaveraceae, Menispermaceae*, and *Ranunculaceae* [232]. Berberine is the principal bioactive ingredient of *Rhizoma coptidis*, a common traditional Chinese herb used for the therapy of inflammatory disorders and diabetes mellitus [233]. Berberine up-regulated SR-BI expression, and inhibited oxLDL-induced foam cell formation from macrophage by inhibiting the lectin-like oxidized LDL receptor-1 (LOX-1) [234].

4.2.3 Trimethylglycine

Trimethylglycine, also called betaine, is a crystalline alkaloid contained in sugar beets and other plants. Betaine serves as an animal and human nutrient, which has been well investigated in respect of its effects on lipid metabolism and CVD, as well as liver disease [235, 236]. Feeding pigs with betaine-supplemented diets during pregnancy and lactation increased hepatic LDLR and SR-BI gene expression [237]. Chronic ethanol markedly inhibited the glycosylation of SR-BI, resulting in the decreased localization of the mature SR-BI in the liver as well as alcoholic hyperlipidemia. Betaine effectively prevented chronic alcohol-mediated impairment of SR-BI glycosylation, plasma membrane localization, and consequent impaired cholesterol uptake function [238].

4.2.4 Clinical study

Several systematic reviews and meta-analyses of randomized controlled trials have consistently demonstrated the beneficial effects of alkaloids on blood cholesterol [230, 239-241]. To date, a number of human trials have been performed on subjects with different disease conditions including those with hypercholesterolemia [242-244], metabolic syndrome [245, 246] and CVD [247]. Meta-analysis of 11 clinical trials (including 874 participants) have revealed that the administration of berberine produced a significant reduction in total cholesterol, triglycerides and LDL cholesterol levels, with a remarkable increase in HDL [248]. The majority of the human trials showed reductions of 11-29% in total cholesterol and 8-25% in LDL cholesterol while a few did not show significant effects [245, 249].

Various human clinical studies have found that in addition to alkaloids' association with metabolic diseases, betaine intake is associated with cancers, such as lung cancer [250] and liver cancer [251]. In these studies, a higher betaine intake resulted in a lower risk of cancer. Furthermore, research has suggested that cancer incidence could be decreased by 11% by consuming choline plus betaine (100 mg/day) [252]. The association between caffeine intake and cancer has been extensively studied. Recently in a clinical trial on prostate, lung, colorectal, and ovarian cancer screening, of the 97,334 eligible individuals, 10,399 developed cancer. Caffeine intake was not associated with cancer risk in a dose-response manner [253].

4.3 Terpenoids

Terpenoids are a group of about 40 000 compounds with diverse structures, all sharing the characteristic of being synthesized from isoprenoid building blocks. According to the number of these isoprene units, Terpenoids of 5, 10, 15, 20, 30 and 40 carbon atoms are classified as hemi-, mono-, sesqui-, di-, tri- and tetra-terpenes, respectively [254]. For instance, the sesquiterpenes isolated from various species of marine sponges exhibited various biological activities. New tetracyclic merosesquiterpenes, including both 19-methoxy-9,15-ene-puupehenol isolated from the marine sponge *Hyrtios digitatus* and the known 20-methoxy-9,15-ene-puupehenol could activate SR-BI in HepG2 cells [255]. Tetraterpenoids, also called carotenoids, comprise a group of tetraterpenes in plants. β-Carotene, the principal provitamin A carotenoid, partly controlled SR-BI activity through a feedback regulation [256]. Indeed, studies have pointed out that SR-BI activity was partly controlled by cleaved β-carotene retinoids. Using both mouse models and human cell lines, it was specifically shown that retinoic acid induced the expression of the intestinal transcription factor intestine-specific homeobox (ISX) that repressed the expression of SR-BI [257], thus impacting both carotenoid conversion and uptake [258]. To the best of our knowledge, there are a large number of *in vitro* studies demonstrating the cytotoxicity of terpenoid molecules against various breast [259], prostate [260] and liver cancer cells [261], yet very few compounds have been evaluated in clinical study.

4.4 Unsaturated fatty acid

Omega-3 fatty acids, such as docosahexaenoic acid (DHA) and eicosapentaenoic acid (EPA), induced higher gene expression of SR-BI, ABCA1, and ABCG5, which might be the mechanisms

by which these compounds increased fecal cholesterol excretion from obese hamster compared to control [262]. Olive oil, containing oleic acid, up-regulated the genes of SR-BI, ABCA1, PPARγ and CD36 [263], which might contribute to the cardiovascular-protective effect of olive oil [263]. 13-hydroxy linoleic acid (13-HODE), which is the hydroxylated derivative of linoleic acid (LA), is a natural PPAR agonist [264]. 13-HODE increased protein levels of SR-BI, LXRα, ABCA1, and ABCG1 in macrophages, and further induced macrophage cholesterol efflux [265].

Dietary guidelines recommended by the American Heart Association (AHA) for health individuals include consumption of omega-3 fatty acids [266]. However, the increase in LDL-cholesterol is a potential disadvantage of omega-3 fatty acids consumption [267, 268]. On the contrary, the COMBOS study revealed a reduction from baseline in non-HDL-cholesterol was significantly greater with omega-3 acid ethyl esters (OM-3A EE) plus simvastatin than with simvastatin alone [269]. Treatment with OM-3-A EE also significantly reduced TG levels and VLDL-cholesterol levels compared with placebo. Many publications indicated the efficacy of omega-3 fatty acids in cancer therapy. In an epidemiological study, women affected by metastatic breast cancer supplemented with 1.8 g of DHA during chemotherapy with anthracyclines could increase their survival by 8 months and decrease symptoms [270]. EPA (2.7 g/day) has been reported to be able to inhibit colorectal aberrant crypt foci, compared to placebo control group after one month of supplementation in a Japanese clinical trial [271]. Due to low side effects, high efficacy, and tolerability against chemotherapy and radiotherapy, a plenty of clinical studies has been performed on prostate, lung, gastric, pancreatic cancer [272].

4.5 Polysaccharides

Guar gum (GG) is a viscous polysaccharide extracted from the seed of the legume plant *Cyamopsis tetragonolobus* that has been reported to have hypocholesterolemic effects in guinea pigs [273], rats [274], and humans [275]. In pigs fed with an atherogenic diet, GG consumption reduced hepatic SR-BI mRNA to 36% of the control expression but did not affect SR-BI protein abundance [276]. β-Glucans comprise a group of β-D-glucose polysaccharides naturally localizing in the cell walls of cereals. It was reported that fungi β-glucan from oat fiber remarkably increased phagocytosis and SR-BI expression in the macrophage, decreased blood levels of LDL-cholesterol (LDL-C) and reduced the risk of CVD [277].

It was shown that flavonoids (*e.g.*, luteolin, quercetin, kaempferol), stilbenes (*e.g.*, resveratrol, amorphastilbol), and unsaturated fatty acids (*e.g.*, omega-3 fatty acids, oleic acid) can be acting as ligands of PPARs, which regulate SR-BI expression as discussion in section 3. It was also reported that the natural chenodeoxycholic acid, isolated from goose bile or *Calculus bovis*, could activate FXR and directly up-regulate SR-BI expression through intron binding on the FXRE [117].

5. Conclusions

SR-BI is a membrane glycoprotein and expressed in many normal and hormonally altered tissues and cell types. SR-BI is critical to lipoprotein metabolism by mediating selective uptake of CE from HDL in liver cells and the bi-directional flux of free cholesterol [16]. SR-BI is emerging as a multifunctional protein, which regulates clearance of remnant lipoproteins and Lp(a), autophagy, efferocytosis, autophagy, apoptosis, inflammation, adrenal steroid synthesis, oxidative stress, uptake of vitamins and viral entry into cells [2], as well as affects gastrointestinal, endocrine, reproductive, and cardiovascular pathophysiology [27-32]. In addition, SR-BI could also serve as a promising target for the delivery of therapeutic agents by reconstituted HDL [19, 20]. There are a number of studies trying to understand the relationship between functions of SR-BI and various diseases, including cancer and CVD.

It has been demonstrated that cholesterol metabolism was changed in cancer cells [61]. Cancer cells can take up CE *via* HDL/SR-BI pathway and use it as the substrate to enhance malignant phenotypes [68, 69]. It was also shown that cholesterol metabolism plays an important role in cancer development and metastasis [66]. Furthermore, the protein expression level of SR-BI was demonstrated to correlate with development of some cancers, such as breast cancer, gastric adenocarcinoma tumor, prostate cancer, colorectal cancer, ovarian cancer and pancreatic cancer [70, 72, 77]. It was indicated that SR-BI plays an important role in cancer cell proliferation and apoptosis, suggesting its effect on carcinogenesis and metastasis. It was also shown that SR-BI regulates proliferation or apoptosis of cancer cells possibly through PI3K/AP-1, Akt or MITF pathways. It still remains to further examine the specific mechanisms for SR-BI involvement in development of cancer. SR-BI accessory protein PDZK1 is also involved in caner. PDZK1 regulated cell growth possibly by mediating c-Myc expression, which is often constitutively expressed in cancer cells. However, whether the effect of PDZK1 on the growth of cancer cells is

dependent on SR-BI needs to be further studied. In addition, TAMs are associated with tumor progression, invasion and metastasis, and poor prognosis [86]. TAMs can switch to a phenotype promoting immunosuppressive function within the tumor microenvironment [87, 88], which may be mediated by SR-BI. The membrane cholesterol efflux of TAMs also influenced TAM-regulated tumorigenesis possibly by PI3K activity or mTORC2. Although SR-BI also mediates membrane cholesterol efflux, it remains to investigate the influence of SR-BI on membrane cholesterol efflux in TAMs and whether reprogramming of TAMs affects tumorigenesis through SR-BI. Although recent studies indicated SR-BI as a potential marker for cancer diagnosis and prognosis [17], it is important to further explore the role of SR-BI in cancer development, and investigate whether SR-BI could be used as a target to treat cancer in the future.

The SR-BI protein expression can be regulated by transcriptional factors, endogenous factors, miRNAs, and its accessory proteins (NHERF1, NHERF2, PDZK1/NHERF3) at the transcriptional, post-transcriptional, or post-translational levels. The transcriptional factors regulating SR-B1 expression include LXRα/β, PPARα/γ, FXR, RXR, SREBP-1a/1c/2, ER-α/β, SF-1, HNF4α, LRH-1, PREB, FoxO1/3/4, DAX-1, YY-1, PXR and STAT1/2. Endogenous factors regulating SR-B1 expression include hormones (ACTH, glucocorticoids, Ang II, insulin, IGF-1, PAPP-A, TRβ, HL, testosterone and leptin), cytokine IFNα, LGF, HSL, and glucose. The regulation of SR-BI expression mediated by transcriptional factors and endogenous factors is very complicated. Some transcriptional factors (such as LXR and PPAR) and endogenous factors (such as ACTH) regulate SR-BI expression not only at the transcriptional level, but also at the post-transcriptional level. Additionally, the regulating effects of some factors (such as LXR, PPAR, FXR, ER, glucocorticoids) on SR-BI expression were inconsistent in literatures, which might be due to the different cell types and different animal models used. The detailed mechanisms of action of many factors regulating SR-BI expression are not clear and need further studies. Recently, several miRNAs, including miR-24, miR-96, miR-125a, miR-185, miR-217, miR-223, and miR-455, have been found to regulate the SR-BI expression. It remains to further explore other miRNA regulating SR-BI expression. Another kind of ncRNA, long ncRNAs (lncRNA), have also been proposed as a new layer of gene regulation, however, up to now there are no studies to report lncRNAs regulating SR-BI expression. In addition, there are no studies to focus on the role of this kind of factors on SR-BI expression in tumor tissues or cells. Accessory proteins, PDZK1/NHERF3, NHERF1 and NHERF2, can interact with SR-BI and regulate the expression of SR-BI at the post-translational level [17]. Decrease in PDZK1 strongly down-regulated the SR-BI expression in liver, kidney and gut, while NHERF1 and NHERF2 overexpression down-regulated the SR-BI protein expression

in liver and steroidogenic tissues/cells. It would be very interesting to investigate the changes of these factors in cancer tissues and cells, and further investigate their effect on SR-BI expression in cancer.

Natural products have been proven to be a promising pool for drug discovery. In this review, we summarized the identified natural products that regulate SR-BI expression, including polyphenols, alkaloids, terpenoids, unsaturated fatty acid, and polysaccharides. The natural products from polyphenols group reported to regulate SR-BI expression include quercetin, kaempferol, catechin, PGG, apigenin-7-O-β-D-glucuronide, luteolin, caffeic acid, ferulic acid, ellagic acid, resveratrol. In addition, caffeine, berberine, trimethylglycine, 19-methoxy-9,15-ene-puupehenol, 20-methoxy-9,15-ene-puupehenol, β-carotene, DHA, EPA, 13-hydroxy linoleic acid, oleic acid, guar gum, and chenodeoxycholic acid from other groups were reported to regulate SR-BI expression. At present, most of the natural products regulating SR-BI expression were identified incidentally by studies examining lipid metabolism. There are no systematic studies screening the effect of natural products on SR-BI expression. In many cases the detailed molecular mechanisms of the studied natural products remain elusive or are just deduced from coincidental observations lacking experimental proof of causality. Thus, in-depth and stringent molecular analyses of active natural products may discover new strategies for the treatment or prevention of human diseases involving SR-BI, including cancer.

SR-BI plays a very important role in regulation of cholesterol metabolism in humans. In clinical studies, polyphenols were reported to exhibit the beneficial effects on hyperlipidemia while contrary opinions also exist. For example, supplementation of flavonoid-rich grape seed extracts and black/green tea, pycnogenol as well as red wine polyphenols were found to have a beneficial effect on plasma lipoprotein and cholesterol. On the contrary, some studies indicated that there was no relationship between polyphenol consumption and the risk of CVD or cholesterol profile. Interestingly, clinical trials have reported that supplementation of polyphenols-rich grape skin extract and flavonoids could reduce biochemically recurrent prostate cancer and ovarian cancer risk, respectively. Systematic reviews and meta-analyses studies have consistently demonstrated administration of alkaloid berberine reduced total cholesterol, triglycerides and LDL cholesterol levels in humans [248]. Moreover, a higher betaine intake was associated with lung cancer [250] and liver cancer [251]. Unsaturated fatty acid omega-3 fatty acids consumption increased in LDL-cholesterol [267, 268], while OM-3A EE significantly reduced TG levels and VLDL-cholesterol levels compared with placebo in humans [269]. Omega-3 fatty acids DHA and EPA were reported

to exhibit therapeutic effects on breast cancer and colorectal aberrant crypt foci, respectively [270, 271]. However, all these clinical studies are not able to prove whether the therapeutic effects of these natural products are due to their regulation of SR-BI expression or not.

Future directions in studying the SR-BI as a target of natural products and its significance in cancer include:

****Further understanding the role of SR-BI in cancer development.** Recent studies indicated SR-BI as a potential marker for cancer diagnosis and prognosis in humans [17], and plays an important role in cancer cell proliferation and apoptosis *in vitro* studies, but it is important to further confirm whether SR-BI could be used as an useful target to treat cancer *in vivo* and finally in humans.

****Further understanding the regulatory mechanisms of SR-BI expression in cancer development by new biotechnologies.** Although significant progress has recently been made in characterizing regulatory mechanisms of SR-BI, there are very limited studies to focus on its regulatory mechanisms in tumor tissues or cells. At present, new biotechnologies including RNA-sequencing, lncRNA arrays, RNA interference (RNAi) or CRISPR/Cas9 library screening, has empowered the discovery of new epigenetic regulators (such as lncRNAs) that are associated with or regulate SR-BI expression [278]. Further investigation of the role of these new regulators will provide us a clear picture of how SR-BI expression is regulated in cancer development and can be therapeutically targeted.

****Systematic studies screening of natural products targeting SR-BI expression in cancer models**. Natural products have been proven to be a promising pool for drug discovery. At present, most of the natural products regulating SR-BI expression were identified incidentally by studies examining lipid metabolism. There are no systematic studies screening the effect of natural products on SR-BI expression. To identify potential drug leads with capability of regulating SR-BI expression in cancer cells or tissues from such large pool, it is important to do systematic screening of natural products targeting SR-BI expression in cancer models by high throughput drug screening platforms.

Declaration of interests

The authors state that there is no conflict of interest.

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Figure 1

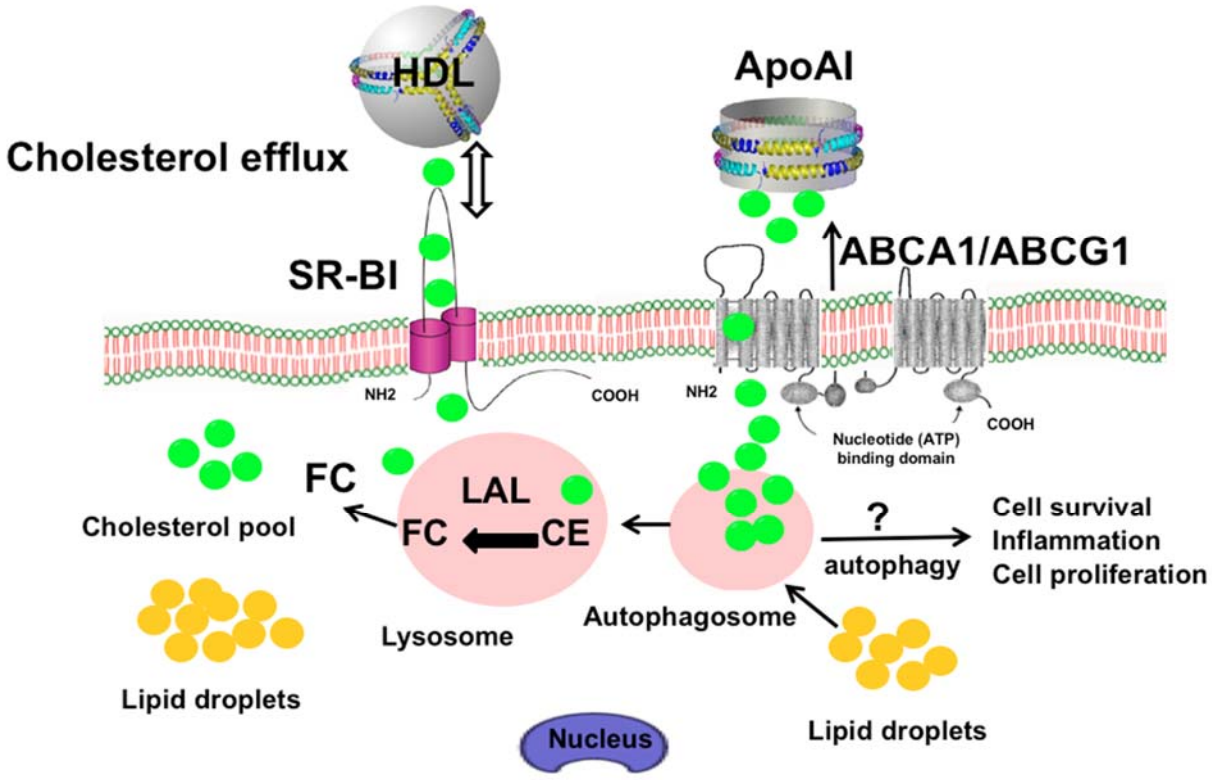


Figure 1. Role of scavenger receptor class B type I (SR-BI) in preventing macrophage foam cell formation by promoting cholesterol metabolism. Three main proteins, including SR-BI, ATP-binding cassette transporter A1 (ABCA1), and ABCG1, mediate the efflux of free cholesterol (FC) in macrophages. SR-BI transports cholesterol to high-density lipoprotein (HDL), whereas ABCA1 effluxes cholesterol to lipid-poor apolipoprotein AI (apoAI) or to apoE which is released by macrophages. There are two pathways to clear cytoplasmic cholesteryl ester (CE): (i) CE is converted by neutral CE hydrolase (NCEH) and the FC transported to the plasma membrane for efflux; (ii) cytoplasmic CE is also trafficked into autophagosomes that fuse with lysosomes, where the CE is converted into cholesterol by lysosomal acid lipase (LAL) and the FC transported for efflux from macrophages.

Figure 2

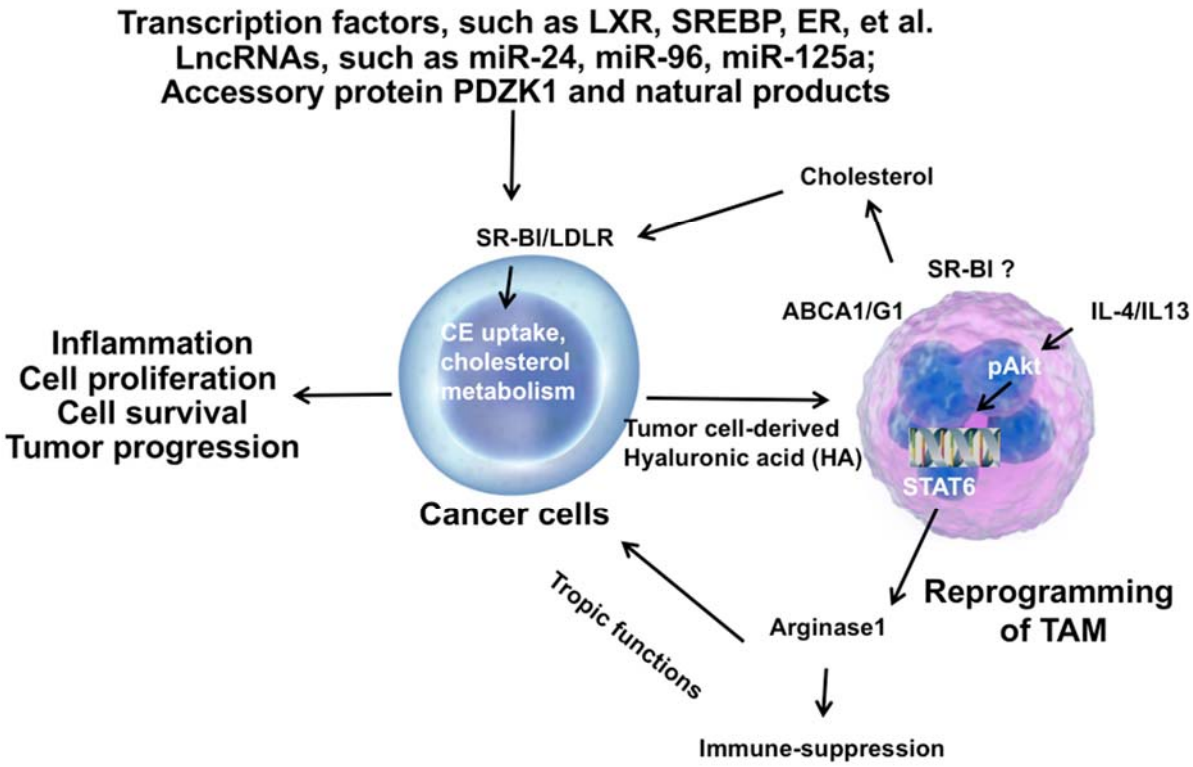


Figure 2. Effects of natural products, transcription factors and LcnRNAs on SRBI expression and reprogramming of tumor-associated macrophages (TAM) through cholesterol efflux in tumor progression. Natural products, transcription factors and LncRNAs regulate the expression of SR-BI, which controls the cholesterol ester uptake in cancer cells. Tumor cell-derived hyaluronic acid (HA) promotes ABCA1-ABCG1-mediated membrane cholesterol efflux in TAM and causes the reprogramming of TAM through p-Akt/STAT3 pathway. IL-4-induced gene expression in TAMs is related to tumor-promoting functions, including increased arginine metabolism and promoting immune suppression and trophic functions, which further results in cancer invasion and metastasis.

Figure 3

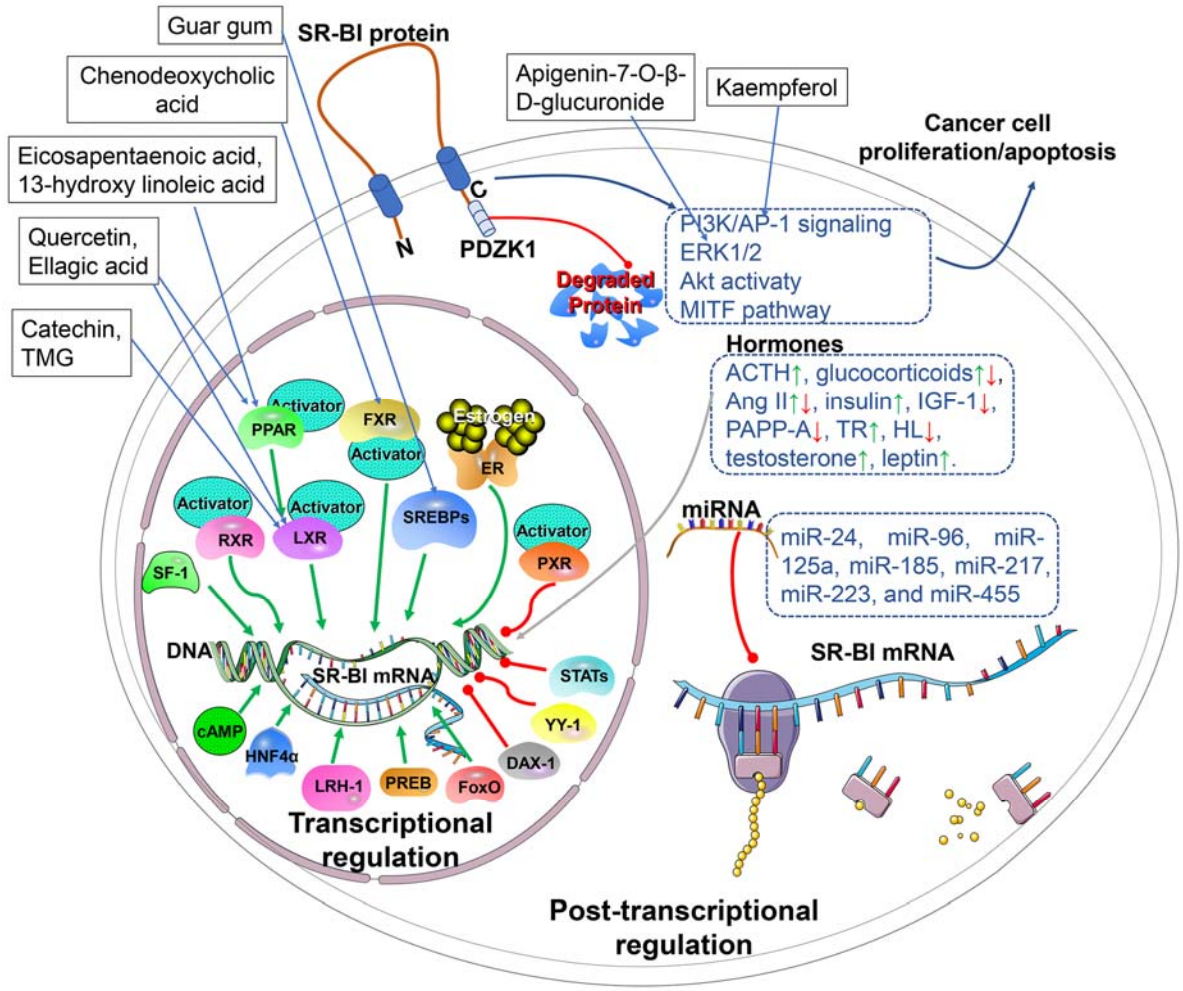


Figure 3. Regulatory mechanisms of SR-BI expression at transcriptional and post-transcriptional and post-translational levels, as well as targets by which natural products regulate SR-BI expression. At the transcriptional level, SR-BI protein expression is regulated by a variety of molecules, including transcription factors (LXRα/β, PPARα/γ, FXR, RXR, SREBP-1a/1c/2, ER-α/β, SF-1, HNF4α, LRH-1, PREB, FoxO1/3/4, DAX-1, YY-1, PXR and STAT1/2), hormones (ACTH, glucocorticoids, Ang II, insulin, IGF-1, PAPP-A, TRβ, HL, testosterone and leptin), miRNAs (miR-24, miR-96, miR-125a, miR-185, miR-217, miR-223, and miR-455), and SR-BI accessory proteins (PDZK1/NHERF3, NHERF1 and NHERF2) (→: Activation; —●: Inhibition).

Table 1. SR-BI variants identified from human subjects with abnormal HDL-C levels

SR-BI variants	Phenotype	References
G2S	Higher levels of HDL-C and lower levels of LDL-C in males, confirmed an increased risk of CHD	[279]
S112F	37% increase in HDL-C in heterozygotes	[280]
SR-BI deletion of 140 −150 11-bp	The deletion allele exhibited higher HDL-C levels	[281]
V135I	Higher HDL-C levels in Amish women	[282]
142C→T Polymorphism	No significant differences in plasma HDL-C levels between the different genotype groups	[281]
T175A	37% increase in HDL-C in heterozygotes	[280]
I179N	Impaired uptake of HDL-CE and increase in atherosclerosis in mice	[283]
G239R	Higher HDL-C, higher TG levels	[284]
P297S	Increase in HDL-C levels and reduction in cholesterol efflux	[39]

A350A, C-T polymophism	Synonymous exon 8 C-T (allelic frequency 48%) polymorphism, A350A, associated with atheroprotection in men, but not in women	[285]
V32M, V111M, G319V	Increase in HDL-C, but not associated with CAD	[286]
P376L	2.8-fold increase of HDL-C in heterzyotes and a 6.1-fold increase in the homozygotes, larger HDL-2b particles, also associated with increased risk of CHD	[58]

Table 2. The factors regulating SR-BI expression

Factors	Cellular models	Animal models and clinical studies
Transcriptional factors		
LXRα and β	↑SR-BI transcription in human and murine hepatoma cell lines, and in 3T3-L1 preadipocytes [97]. ↓SR-BI in Caco-2/TC7 cells *via* a post-transcriptional mechanism [98].	↑mRNA and protein levels of SR-BI in hamster liver [99]. ↓SR-BI protein, not mRNA levels in hepatic membranes of C57Bl/6J mice [100].
PPARα	↑SR-BI levels in rat hepatocytes and HepG2 hepatoma cells, as well as liver endothelial cells [103].	↑Hepatic SR-BI expression in hamsters [104], and in atherosclerotic lesions of apoE-deficient mice [105]. ↓SR-BI protein expression in the liver in both wild-type C57BL/6 mice [106] and PDZK1-deficient mice [107]. No change in SR-BI mRNA level in circulating mononuclear cells in humans [108].
PPARγ	↑SR-BI expression in rat hepatocytes, endothelial cells, Hepa 1c1c-7 and Kupffer cells [103], as well as in HepG2 [109].	↑SR-BI protein expression in adipose tissue, but not liver in C57BL/6 mice [110], as well as in atherosclerotic lesions of apoE-deficient mice [105].

FXR	↑mRNA and protein levels of hepatic SR-BI [115]. ↓SR-BI expression in hepatocytes [111], and Huh7.5 cells [114].	↑hepatic SR-BI mRNA and protein levels in hyperlipidemic hamsters, but not in normolipidemic hamsters [116].
RXR	↑SR-BI mRNA in HUVECs [120].	N.A.[1)]
SREBP-1a and c	↑SR-BI gene expression by activation of SREBP-1a [123].	↓hepatic SR-BI in SREBP-1a and -1c transgenic mice on normal chow [125].
SREBP-2	↑SR-BI mRNA and protein levels in transfected HEK293 and HepG2 cells [124].	N.A.
ER	↑SR-BI promoter activity by activation of ER-α and -β by binding to ER element [123]. ↓Endothelial SR-BI in human coronary artery endothelial cells [129].	↑SR-BI in the adrenal gland and corpus luteal cells of the ovary in rats [127]. ↓SR-BI in the liver and the ovary in rats [127].
SF-1	↑SR-BI gene expression in both human HTB9 bladder carcinoma and mouse Y-1 tumor cells [132].	No SR-BI mRNA in the gonadal ridge of day 11.5 SF-1 KO embryos [133].
HNF4α	↑SR-BI expression at both mRNA and protein levels in cultured hepatocytes [134].	↑SR-BI mRNA and protein levels in the liver in rat
LRH-1	↑SR-BI expression *in vitro* [135].	↓SR-BI mRNA levels in livers of the heterozygous LRH-1-KO mice [135].

PREB	↑SR-BI protein in the adrenocortical cell line Y-1 [137].	N.A.
FoxO	N.A.	↓hepatic SR-BI expression in the mice with liver-specific triple FoxO KO (FoxO1,3,4) [138].
DAX-1	↓SR-BI promoter activity in transfected adrenal Y-1, HTB-9, and HepG2 cells [139].	N.A.
YY-1	↓activity of the SR-BI promoter in transfected HTB9 cells [141].	N.A.
PXR	↓SR-BI in HepG2 cells and in primary rat hepatocytes [142].	↓hepatic SR-BI level in ApoE3-Leiden (E3L) and E3L.CETP mice [143].
STAT	↓SR-BI promoter activity upon mutagenesis of a STAT1/STAT2 response element in the SR-BI promoter [137].	N.A.
Endogenous factors		
ACTH	↑SR-BI protein and mRNA expression in the cultured murine Y1-BS1 adrenal cells [17].	↑SR-BI protein expression in adrenal glands in C57BL/6 mice [147].
Glucocorticoid	↓SR-BI expression in adrenocortical H295R and ovarian SKOV-3 cells [150]. ↑SR-BI mRNA expression in primary rat hepatocytes by a glucocorticoid dexamethasone [151].	↓SR-BI gene expression in adrenals of corticosterone-deficient mice [150].

	No effect in HepG2 cells and THP-1 macrophages treatment with dexamethasone [151].	
Angiotensin II	↓SR-BI expression in human umbilical vein endothelial cells [152], and the mouse proximal tubular cell line MCT cells [153]. ↑SR-BI mRNA and protein expression in the human adrenocortical carcinoma cell line NCI-H295R cells [154].	↓SR-BI protein expression in isolated tubules of rats [153].
Insulin	↑SR-BI mRNA and protein levels in polarized CaCo-2 cells [155].	↑SR-BI expression in all intestinal segments in two diet-induced animal models of insulin resistance (fructose-fed hamster and high-fat-fed mouse) [156].
IGF-1	↓SR-BI mRNA and protein levels in THP-1-derived macrophages [157], and in cultured HepG2 cells [158].	↓SR-BI mRNA level in rats [158].
PAPP-A	↓SR-BI expression in THP-1 macrophage-derived foam cells [158].	↑SR-BI expression in both aorta and peritoneal macrophages in apoE-deficient mice with PAPP-A knockdown [159].
TRβ	↑SR-BI expression [160].	N.A.
HL	↑SR-BI expression in adrenal gland in mice when inhibition of HL [161, 162].	N.A.
Testosterone	↑SR-BI mRNA and protein levels in both cultivated HepG2 cells and primary human monocyte-derived macrophages (HMDMs) [163].	N.A.

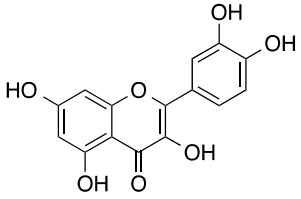
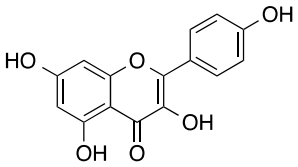
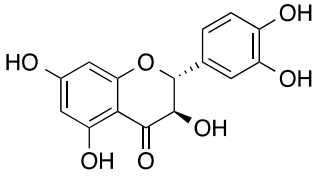
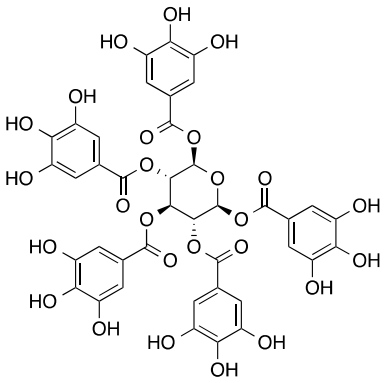
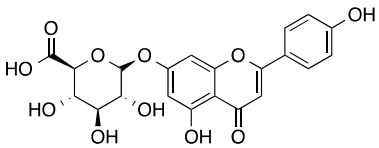
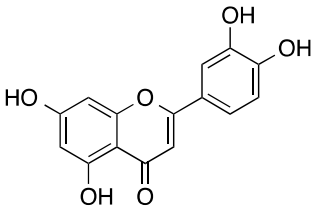
Leptin	N.A.	↑hepatic SR-BI protein and mRNA levels in leptin-deficient mice [164].
IFNα	↓SR-BI expression in HepG2 [144].	N.A.
cAMP	↑SR-BI mRNA expression in transfected 293T cells, human granulosa SVOG-4o cells, and in primary cultures of rat theca-interstitial cells [166].	N.A.
LGF	N.A.	↑SR-BI protein level in ethane dimethanesulfonate (EDS)-treated rats [167].
HSL	N.A.	↑SR-BI protein expression, but not mRNA levels in the testis of hormone-sensitive lipase (HSL) KO male mice [168].
Glucose	↓SR-BI mRNA and protein levels in HMDMs [169], Caco-2/15 cells [170], and HepG2 cells [171] upon treatment with high glucose (25-30 mM). ↑SR-BI mRNA and protein expression in J774A.1 macrophage-like cells upon treatment with high glucose (30 mM) [172]. No changes in SR-BI abundance in polarized CaCo-2 cells upon treatment with high glucose [155].	↑SR-BI mRNA and protein expression in mouse peritoneal macrophages (MPM) harvested from C57Bl/6 diabetic mice, compared to MPM from control non-diabetic mice [172].
Noncoding RNAs (ncRNA)		

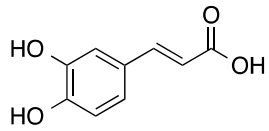
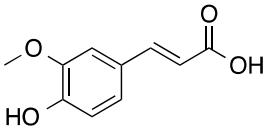
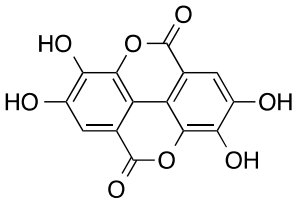
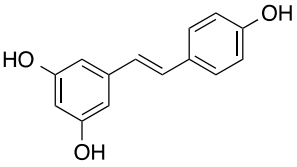
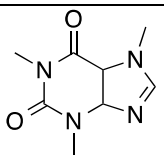
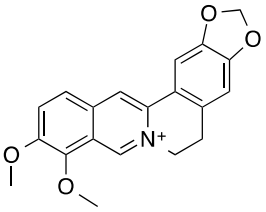
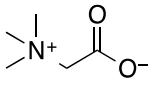
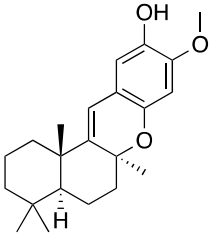
miR-24	↓SR-BI protein expression in HepG2, THP-1 cells [173], steroidogenic cells MLTC and Y-1, and HepG2 cells [174].	↓hepatic SR-BI expression in apoE-deficient mice [173].
miR-96	↓level of SR-BI expression in HepG2 cells [175].	↑SR-BI in the liver of apoE-deficient mice with a high fat diet (HFD) when decrease of miR-96 [175].
miR-125a	↓mRNA and protein levels of SR-BI in the rat Leydig tumor R2C cells, the cAMP-sensitive MLTC cells [176], and mouse hepatic cell line Hepa 1-6 [176], as well as mouse and rat liver cells [176].	N.A.
miR-185	↓level of SR-BI expression in HepG2 cells [175].	↑SR-BI in the liver of apoE-deficient mice with a HFD when decrease of miR-185 [175].
miR-217	N.A.	↓SR-BI mRNA levels in apoE-deficient mice [177].
miR-223	↓level of SR-BI expression in HepG2 cells [175].	
miR-455	↓mRNA and protein levels of SR-BI in the rat Leydig tumor R2C cells and the cAMP-sensitive MLTC cells [176]. Does not influence expression of SR-BI in mouse and rat liver cells [176].	N.A.
Accessory proteins		

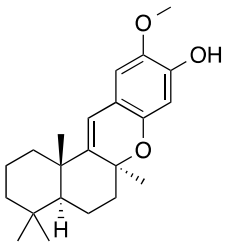
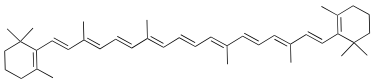
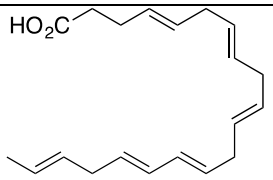
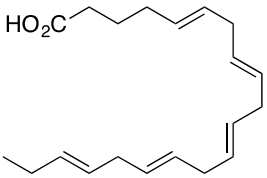
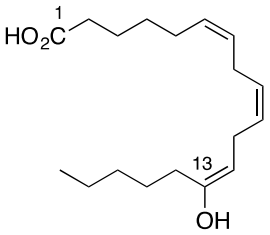
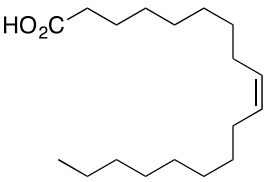
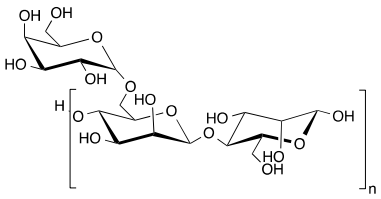
NHERF1	↓SR-BI protein expression in liver and steroidogenic cells [180].	↓SR-BI protein expression in liver and steroidogenic tissues [180].
NHERF2	↓SR-BI protein expression in liver and steroidogenic cells [180].	↓SR-BI protein expression in liver and steroidogenic tissues [180].
PDZK1/NHERF3	↑SR-BI expression at the post-translational level *in vitro* [17].	↓SR-BI protein expression in PDZK1-deficient mice in the liver and the proximal intestine [178]. Not affected SR-BI expression in steroidogenic organs in mice [178].

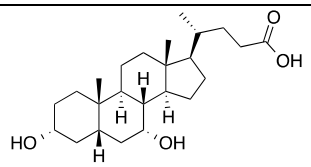
[1)] N.A. = not applicable.

Table 3. Natural products regulating SR-BI expression

Classification	Sub-classes	Compounds	Structures	References
Polyphenols	Flavonols	Quercetin		[190]
		Kaempferol		[191]
	Flavanols	Catechin		[287]
	Gallotannin	1,2,3,4,6-Pentagalloyl glucose (PGG)		[193]
	Flavones	Apigenin-7-*O*-β-D-glucuronide		[195]
		Luteolin		[196]

	Phenolic acids	Caffeic acid		[198]
		Ferulic acid		[198]
		Ellagic acid		[199]
	Stilbenes	Resveratrol		[204] [205]
Alkaloids	Purine alkaloids	Caffeine		[231]
	Benzylisoquinoline alkaloids	Berberine		[234]
	Betaine	Trimethylglycine (TMG)		[237, 288]
Terpenoids	Sesquiterpenes	19-methoxy-9,15-ene-puupehenol		[255]

		20-methoxy-9,15-ene-puupehenol		[255]
	Tetraterpenes (Carotenoids)	β-Carotene		[256]
Lipids	Unsaturated fatty acids	Docosahexaenoic acid (DHA)		[262]
		Eicosapentaenoic acid (EPA)		[262]
		13-hydroxy linoleic acid		[265]
		Oleic acid		[263]
Polysaccharides	Galactomannans	Guar gum (guaran)		[276]

Bile acids	Primary bile acids	Chenodeoxycholic acid		[117]